

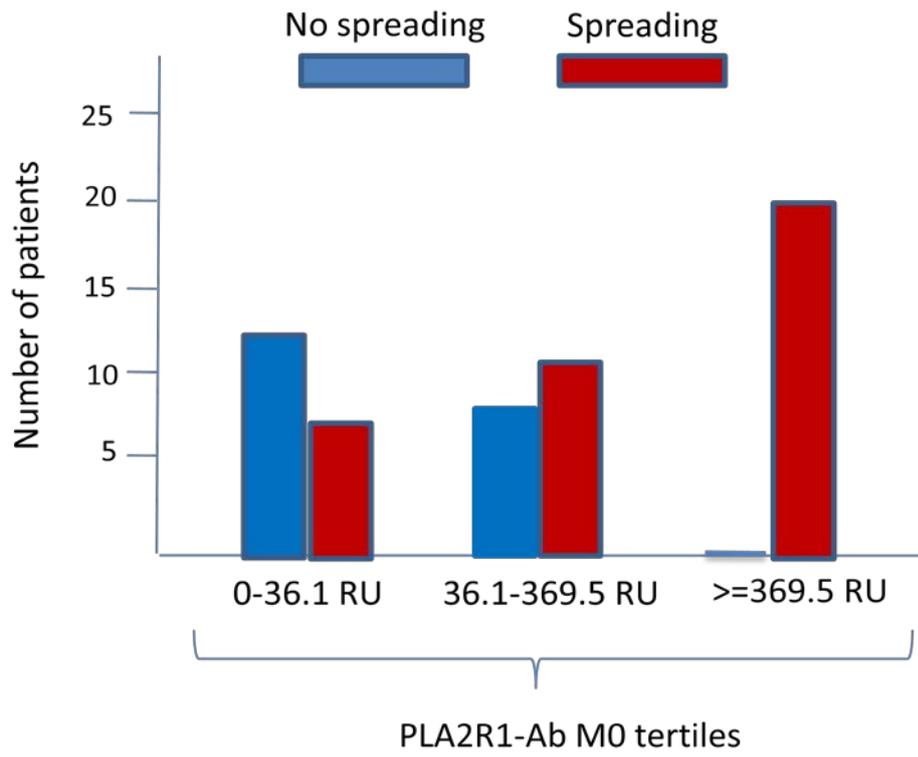
Supplementary appendix

Supplementary Note #1: Patients' inclusion and non-inclusion criteria in the GEMRITUX study¹¹

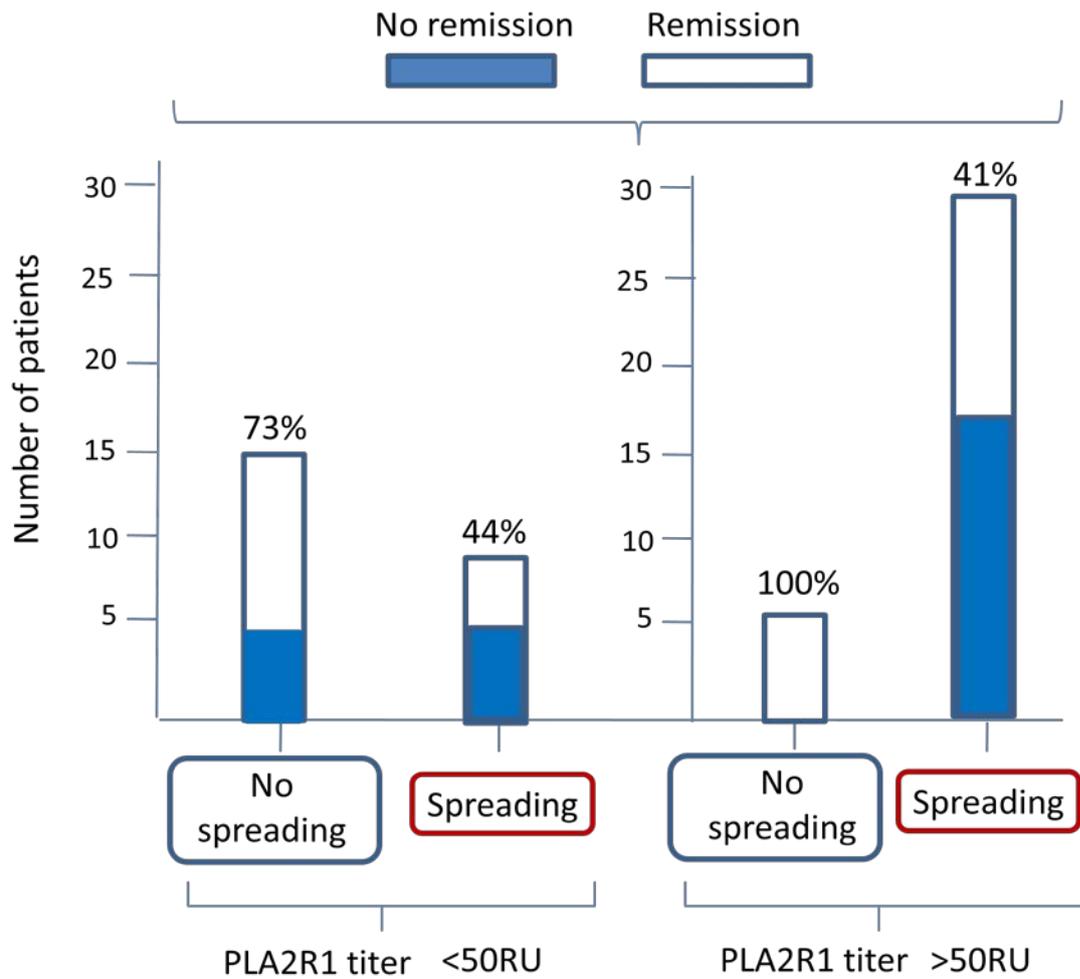
Eligible patients were 18 years of age or older and had a biopsy-proven primary MN (pMN). Patients were enrolled from January 2012 to July 2014 in 31 French centers if they had a urinary protein excretion or a urinary protein/creatinine ratio greater than, or equal to, 3.5 g/day or 3,500 mg/g, respectively, and a serum albumin lower than 30 g/L for at least 6 months despite full dose of Non Immunosuppressive, Antiproteinuric Treatment (NIAT) (angiotensin-converting enzyme inhibitors and/or angiotensin-2 receptor blockers, diuretics and statin). The estimated GFR by MDRD formula had to be above 30 mL/min/1.73m². Exclusion criteria were secondary MN, pregnancy, breast-feeding, immunosuppressive treatment in the three preceding months, and active infectious disease.

Supplementary Note #2: Clinical and immunological remission

Clinical remission was defined accordingly to 2012 KDIGO (KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl.*2: 186-197, 2012) as 1) complete in case of urinary protein excretion less than 500 mg per day or 500 mg/g creatinine; 2) partial in case of urinary protein excretion <3.5 g per day or 3,500 mg/g creatinine and \geq 500 mg/g creatinine with at least 50% reduction compared to baseline. Antibody depletion was defined as complete disappearance of antibodies in PLA2R1-Ab positive patients.



Supplementary Figure 1: Rate of spreading according to PLA2R1-Ab titer.



Supplementary Figure 2: Rate of remission at last follow-up according to antibody titer and epitope spreading. The numbers above the bars indicate the % remission in the various combinations.

Supplementary Table 1: Association of epitope group with clinical characteristics of the GEMRITUX cohort (n=58) at baseline.

Characteristics at baseline	Negative n=4	CysR n=16	CysRC1 n=8	CysRC7 n=10	CysRC1C7 n=20	P value
Age	58.5 [43.5 ; 62.0]	57.5 [43.5 ; 62.0]	47.5 [38.5 ; 64.0]	48.5 [41.0 ; 64.0]	59.5 [41.5 ; 63.5]	0.9391
Time from diagnosis to inclusion (months)	8.0 [6.0 ; 17.5]	8.0 [6.5 ; 17.5]	7.0 [6.0 ; 8.0]	8.0 [6.0 ; 11.0]	8.5 [6.0 ; 10.0]	0.8019
Gender						
Male	15 (75.0)	11 (68.75)	6 (75.00)	6 (60.00)	15 (75.00)	0.8118
Female	5 (25.0)	5 (31.25)	2 (25.00)	4 (40.00)	5 (25.00)	
Anti-PLA2R1 antibody (RU/mL)	31.6 [18.0 ; 54.4]	33.7 [18.0 ; 54.4]	292.9 [109.6 ; 1085.0]	469.4 [35.1 ; 710.0]	359.0 [58.2 ; 1066.5]	0.0002
Proteinuria (g/g of Creat)	7.9 [3.5 ; 8.5]	7.3 [3.5 ; 8.4]	9.4 [6.4 ; 12.9]	9.7 [6.8 ; 11.7]	7.0 [5.2 ; 9.6]	0.1639
Albuminemia (g/dL)	2.2 [2.0 ; 2.6]	2.3 [2.1 ; 2.8]	1.9 [1.7 ; 2.3]	2.3 [2.1 ; 2.7]	2.0 [1.7 ; 2.5]	0.2976

Creat, serum creatinine

Data are shown as n (%) or median [IQR].

Patients were divided into 4 epitope groups

Supplementary Table 2: Association of epitope spreading with clinical characteristics of the GEMRITUX cohort (n=58) at baseline.

Characteristics at baseline	No spreading n=20	Spreading N=38	P value
Age	58.5 [43.5 ; 62.0]	52.0 [41.0 ; 64.0]	0.8386
Time from diagnosis to inclusion (months)	8.0 [6.0 ; 17.5]	8.0 [6.0 ; 9.0]	0.4987
Gender			
Male	15 (75.0)	27 (71.05)	1
Female	5 (25.0)	11 (28.95)	
Anti-PLA2R1 antibody (RU/mL)	31.6 [18.0 ; 54.4]	376.9 [75.8 ; 746.5]	<.0001
Proteinuria (g/g of Creat)	7.9 [3.5 ; 8.5]	8.3 [6.2 ; 10.4]	0.1649
Albuminemia (g/dL)	2.2 [2.0 ; 2.6]	2.1 [1.8 ; 2.5]	0.5252

Creat, serum creatinine

Data are shown as n (%) or median [IQR].

Patients were divided into “no spreading” (CysR only patients) and “spreading” (at least one additional epitope to CysR) groups.

Supplementary Table 3: Comparison of epitope reactivity subtypes at various timepoints between the NIAT only group and the NIAT-Rituximab group

	NIAT			NIAT+RITUX		
	M0	M3	M6	M0	M3	M6
Negative	0	0	0	0	12	17
CysR	11	7	12	9	3	2
CysRC1	4	6	4	4	3	1
CysRC7	6	3	2	4	3	0
CysRC1C7	8	7	6	12	5	6
Total	29	23	24	29	26	26

Supplementary Table 4: Clinical and immunological characteristics of patients according to outcome at M6

Characteristics	Remission n=15	No remission n=43	P value
Age	58.0 [43.0 ; 63.0]	51.0 [41.0 ; 63.0]	0.4966
Gender			
Male	11 (73.33)	31 (72.09)	1
Female	4 (26.67)	12 (27.91)	
Proteinuria (g/g of Creat) M0	7.4 [3.6 ; 12.8]	8.2 [5.6 ; 9.8]	0.9859
Albuminemia (g/dL) M0	2.1 [1.7 ; 2.4]	2.2 [1.9 ; 2.6]	0.6645
Anti-PLA2R1 antibody (RU/mL)M0	35.4 [24.2 ; 216.3]	199.5 [35.1 ; 538.5]	0.1435
Anti-CysR(RU/mL)	369.0 [258.0 ; 2710.0]	1575.0 [528.0 ; 3356.0]	0.0796
Anti-CTLDD1(RU/mL)	16.0 [0.0 ; 257.0]	424.0 [0.0 ; 3477.0]	0.1748
Anti-CTLDD7(RU/mL)	30.0 [0.0 ; 223.0]	272.0 [48.0 ; 706.0]	0.0098
Epitope group M0			0.0809
CysR	9 (60.00)	11 (25.58)	
CysRC1	2 (13.33)	6 (13.95)	
CysRC7	2 (13.33)	8 (18.60)	
CysRC1C7	2 (13.33)	18 (41.86)	
Spreading M0	6 (40)	32 (74.42)	0.0262
Anti-PLA2R1 antibody (RU/mL) M3*	0.0 [0.0 ; 30.5]	55.9 [16.2 ; 137.8]	0.0093
Epitope group M3**			
Negative	6 (46.15)	6 (16.67)	
CysR	5 (38.46)	5 (13.89)	0.0130
CysRC1	0 (0.00)	9 (25.00)	
CysRC7	0 (0.00)	6 (16.67)	
CysRC1C7	2 (15.38)	10 (27.78)	
Spreading M3 **	2/13(13.33)	25/36(58.14)	0.0011
Treatment			
NIAT	6 (40.0)	23(53.5)	0.55
RITUX	9 (60.0)	20(46.5)	

*: 8 missing values, **: 9 missing values.Creat, serum creatinine

Data are shown as n (%) or median [IQR].

Note that lack of remission was associated with higher level of anti-CTLDD7 antibody and higher rate of spreading at baseline whereas PLA2R1-Ab titer did not reach statistical significance.

Supplementary Table 5: Clinical and immunological characteristics of patients according to outcome at last follow-up

Characteristics	Remission n=32	No remission n=26	P value
Age	56.5 [43.5 ; 63.0]	53.5 [39.0 ; 64.0]	0.6857
Gender			
Male	19 (73.08)	23(71.88)	1
Female	7 (26.92)	9 (28.13)	
Proteinuria (g/g of Creat) M0	7.9 [4.3 ; 10.1]	8.3 [6.3 ; 9.7]	0.6353
Albuminemia (g/dL) M0	2.1 [1.9 ; 2.6]	2.2 [1.9 ; 2.5]	0.6402
Anti-PLA2R1 antibody (RU/mL) M0	63.1 [26.9 ; 304.6]	363.7 [37.9 ; 710.0]	0.0967
Anti-CysR (RU/mL)	963.5 [276.0 ; 2141.0]	2139.5 [959.0 ; 3356.0]	0.0358
Anti-CTLD1 (RU/mL)	12.5 [0.0 ; 847.0]	1730.5 [12.0 ; 5803.0]	0.0065
Anti-CTLD7 (RU/mL)	81.5 [14.5 ; 259.5]	473.0 [36.0 ; 1115.0]	0.0143
Epitope group M0			0.0196
CysR	16 (50.00)	4 (15.38)	
CysRC1	3 (9.38)	5 (19.23)	
CysRC7	6 (18.75)	4 (15.38)	
CysRC1C7	7 (21.88)	13 (50.00)	
Spreading M0	16(50)	22(84.62)	0.0114
Anti-PLA2R1 antibody (RU/mL) M3*	0.0 [0.0 ; 49.1]	102.5 [41.1 ; 325.9]	0.0006
Epitope group M3**			0.0007
Negative	11 (37.93)	1 (5.00)	
CysR	9 (31.03)	1 (5.00)	
CysRC1	3 (10.34)	6 (30.00)	
CysRC7	3 (10.34)	3 (15.00)	
CysRC1C7	3 (10.34)	9 (45.00)	
Spreading M3**	9/29 (31.03)	18/20(90.0)	< 0.0001
Treatment			0.1964
NIAT	13(40.6)	16(61.5)	
RITUX	19(59.4)	10(38.5)	

*8 missing values; ** 9 missing.Creat, serum creatinine

Data are shown as n (%) or median [IQR].

Note that lack of remission was associated with spreading at baseline and M3, and PLA2R-Ab titer at M3.